Remarks

Applicant notes the withdrawal of Claims 24 - 26. These Claims have been cancelled. The Applicant, however, reserves the right to file one or more divisional applications concerning the subject matter of these claims. Applicant has added new Claim 27, which depends from independent Claim 11, and adds a feature that the recombinant nucleic acid will be at least 5kb. As a result, the Applicant respectfully requests consideration of new Claim 27. Support for new Claim 27 can be found on page 4, paragraph 18. As a result no new matter has been added.

Response to Claim Objections Under 35 U.S.C. §102

Claims 11 and 14 – 23 have been rejected under 35 U.S.C. §102(b) as being anticipated by Sobczak et al. (Eur. J. Biochem., Vol. 175, pp. 379 – 385, 1988). Applicant respectfully submits that Sobczak et al., fails to disclose, either implicitly or explicitly, the construction of circularized recombinant vectors. It is respectfully submitted that the current office action has improperly characterized the teaching of Sobczak et al. The introductory paragraph of Sobczak et al., does not state what the reference is attempting to teach, but rather is utilized to introduce the field of intra and intermolecular ligation. The current office action asserts that because Sobczak et al., states, "insertion of foreign DNA into plasmid requires not only intermolecular but also intramolecular ligation of DNA to allow circularization" the reference therefore teaches constructing circularized vectors in the presence of compaction agents. However, the very next sentence of Sobczak et al. states "In contrast, cloning in lambda vectors requires efficient intermolecular ligation together with the inhibition of intramolecular ligation." This second sentence, taken in the context of the entire paper, clearly reveals to one skilled in the art that Sobczak et al. worked with linear DNA in the

production of linear molecules, particularly lambda vectors. It is well established that each prior art reference must be evaluated as an entirety, and that all of the prior art must be evaluated as a whole. Panduit Corp. v. Dennison Manufacturing Co., 227 USPQ 337 (CA FC 1985); W.L. Gore & Assocs., Inc. v. Garlock, Inc., 727 F.2d at 1550, 220 USPQ at 311 (CA FC 1983); and In re Kuderna, 426 F.2d 385, 390, 165 USPQ 575, 578-79 (CCPA 1970). The court in Panduit Corp. went on to note that "in its consideration of the prior art, however, **the district court erred . . . in considering the claims in less than their entireties . . . and in considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand.**" Panduit Corp, 227, USPQ, at 345 [Emphasis added].

A study of the Materials and Methods section of Sobczak et al., further illustrates the use of linear DNA in the production of linear molecules (i.e., concatemers). Sobczak et al. used pBR322 as a source of linear DNA and illustrated that histone H1 stimulated intermolecular ligation (correlates to linear vector construction), while inhibiting intramolecular ligation (correlates to circularization).

As stated above, one skilled in the art readily understands that intramolecular ligation produces circularization, while intermolecular produces concatemerization. (See, Legerski et al., J. Mol Biol. 181, 297-312, (1985); and Dugaicczyk et al., J. Mol. Biol. 96, 177-184). Applicant respectfully submits that Sobczak et al. demonstrate increasing Histone H1 concentration to stimulate intermolecular ligation, that is the formation of concatemers.

The Examiner is kindly asked to consider Fig. 4 of Sobczak et al., which shows that only concatemers appear on the gel after the ligation reaction was performed in the presence of H1. No

circularized forms appeared. (see ccc lane in Fig. 4). Moreover Fig. 5 of Sobczak et al. shows the same results when using other core histones. As further support, the Examiner is invited to consider the following passage from Sobczak et al., which states:

> Comparison of the respective effects of poly(ethyleneglycol), DNA concentration and histone H1 indicates that, at first sight, they all seem to act in a similar manner: They increase the rate and the extent of ligation and they **largely favor intermolecular over intramolecular ligation.**
>
> The practical applications of ligase stimulation are mainly concerned with the construction of recombinant DNA. Thus, in cloning experiments that require circularization, a low DNA concentration (20 μ/ml) and a low concentration of additive agent [poly(ethyleneglycol) <7.5%] will be favorable. On the other hand, closing in vectors that require the formation of large concatemers will be favored by (a) high DNA concentrations (300 μg/ml) or (b) low DNA concentrations (20 μ/ml and the addition of agents such as poly(ethyleneglycol) (10%) and histone H1 (H1/DNA ratio = 0.28 – 0.34 by mass).

It is respectfully submitted that one skilled in the art would readily recognize that Sobczak et al. demonstrated the exact inverse effect of histones as compaction agents as compared to what the Applicant has demonstrated. The court in In re Gurley , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) acknowledged that "[A] reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."

Applicant respectfully submits that Sobczak et al. teaches away from the use of histones as compaction agents for the creation of circularized vectors. Sobczak et al. demonstrated that histone H1 is only beneficial for concatemerization, not circularization. In fact, the Applicant has demonstrated that "the histone H1, of different structure and not being a histone forming the octamer, but rather a sealing histone, used by itself does not appear to yield results as good as the other histones. This is explained by the fact that, because of its different structure, each one does

not bind to linear DNA, but rather preferably to supercoiled DNA (Van Holde et al., Biophysical Journal, 1987, 72,pp 1388 – 1395)." (Paragraphs 0028 and 0029 of the Applicant's Specification). One skilled in the art, upon reading Sobczak et al., would not attempt to use histones as compaction agents in the construction of circularized vectors.

In conclusion, it is clear that Sobczak et al. demonstrate the exact inverse effect of histone as is described in this application. In this application, compaction agents such as histones are used to stimulate intramolecular ligation to prepare circularized recombinant nucleic acids, whereas Sobczak et al. demonstrates that increasing the concentration of histone H1 stimulates intermolecular ligation, i.e., formation of concatemers and not circularized molecules.

Therefore, Applicant respectfully submits that Sobczak et al. fails to anticipate the method of the solicited claims. Withdrawal of the rejection of claims 11, and 14-23 under 102 U.S.C. § 102 is respectfully requested.

Rejections Under 35 U.S.C. §103

Claims 12 and 13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Sobczak et al., in view of Gaffney et al. (US 5,710,031). As was articulated above, Sobczak et al. teaches that histones must only be used as compaction agents in intermolecular ligation for the construction of linear molecules.

Applicant respectfully submits that the initial burden of showing *prima facie* obviousness is on the PTO. Applicant respectfully submits that nowhere in the current Office Action or any of the previous Office Actions has there been factual evidence showing motivation or desire to modify the vectors as described in Gaffney et al., with the ligation technique employed in Sobczak et al.

Furthermore, no evidence has been provided, which illustrates that the ligation technique described in Sobczak et al. would be effective to ligate and create the vectors as described in Gaffney et al. Applicant respectfully submits that the CAFC has consistently critiqued the Board and the Patent and Trademark Office for not providing such factual evidence. See *In re Lee*, 61 USPQ 1430 (Fed. Cir. 2002). There must be evidence that a skilled artisan confronted with the same problems which face the inventor, and without knowledge of the claimed invention, would select elements from both Gaffney and Sobczak et al. for the combination claimed by the Applicant. *Eco Lochem Inc. v. Southern California Edison Co.*, 56 USPQ2d, 1065 (Fed. Cir. 2000).

In applying these principles to the amended claims, Applicant respectfully invites the Examiner's attention to the following passage of the Applicant's Specification, which articulates the difficulties and uncertainties inherent in creating a large recombinant nucleic acid vector when it states:

> Recombinant vector construction, comprising insertion of a DNA fragment in a vector, includes an *in-vitro* vector reclosure step. In order for reclosure to take place, the ends of the finished vector must be close to each other. These ends move within a sphere with a radius equal to the length of the fragment and with one of the ends as its center. The greater the size of the finished vector, the greater the volume of this sphere. Consequently, the probability of conjunction of the two ends decreases with the length of the finished vector.
>
> With regard to insertion of the fragment in the vector, it takes place if the probability of conjunction between the ends of the insert and those of the original vector is high. Thus, insertion is dependent on the concentration of ends.

Moreover, until the Applicant's claimed invention, people skilled in the art did not recognize the use of histones for the compaction of DNA and subsequent construction of large recombinant vectors.

Furthermore, the Applicant respectfully submits that pVK100 as described in Gaffney et al. is a cosmid-cloning vector. For the Examiner's convenience, we enclose a copy of Dorsey et al. (2003) which shows, at Table 1, that pVK100 is a cosmid-cloning vector. The Examiner's attention is kindly invited to consider paragraph 0008 of the Applicant's Specification, wherein the Applicant describes the inherent limitations of cosmid vectors.

The cosmid technique described in Gaffney et al., can be summarized as follows:

Linearization of the cosmid vector pVK100 with XhoI restriction enzyme in the cos site;

Ligation in the cos site of the 20-30kb fragment and the linearized cosmid;

Packaging the linear DNA thus obtained in the lambda phage; and

Infecting E.coli bacteria with the lambda phage;

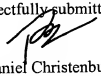
Circularization of the introduced linear DNA, which appears in vivo (inside) the bacteria.

Applicant respectfully submits that one skilled in the art is well aware of this technique, and its inherent limitations. Furthermore, the Applicant respectfully submits that one skilled in the art would also recognize that the technique described above when hypothetically combined with the teaching of Sobczak et al. would not give rise to the claimed invention.

The limitations inherent in the utilization of cosmid vectors would clearly discourage one skilled in the art to use histones, albeit the histone H1 of Sobczak et al., to ligate and construct a large circular recombinant nucleic acid vector. Withdrawal of the rejection based on Sobczak et al., in view of Gaffney et al., is respectfully requested.

In view of the foregoing, Applicant respectfully submits that the Application is now in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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